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(54) Title: THIO-CARBOSTYRIL DERIVATIVE, ITS N-OXIDES AND THE N-OXIDES OF ARIPIPAZOLE

(57) Abstract: The novel thio-carbostyryl derivative 7-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione, its N-oxides and the N-oxides of Aripiprazole and salts thereof are useful agents for treating schizophrenia, Huntington's disease and dyskinesias in Parkinson's disease.

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THIO-CARBOSTYRIL DERIVATIVE, ITS N-OXIDES AND THE N-OXIDES OF ARIPIPRAZOLE

DESCRIPTION

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Field of the invention

The present invention relates to a novel thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole. More particularly, the invention relates to a novel thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole and salts thereof, processes for preparing said thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole and salts thereof, as well as pharmaceutical compositions for treating e.g. schizophrenia containing, as the active ingredient, said thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole or salts thereof.

Background of the invention

20

Schizophrenia is the most common type of psychosis caused by an excessive neurotransmission activity of the dopaminergic nervous system in the central nervous system. [Cf. "Hypothesis of Excessive Dopamine" by Michio Tohrû: TAISHA (Metabolism), Vol. 22, pp. 49, (1985); and Pharmacia Review, No. 10, "KOKORO-TO-KUSURI (Mind and Drugs)" edited by Pharmaceutical Society of Japan]. For a recent review on schizophrenia, see: INTERACTIONS BETWEEN MONOAMINES, GLUTAMATE, AND GABA IN SCHIZOPHRENIA: New Evidence, by Arvid Carlsson, Nicholas Waters, Susanna Holm-Waters, Joakim Tedroff, Marie Nilsson, and Maria L. Carlsson, Annu. Rev. Pharmacol. Toxicol. 2001, 41:237-60.

A number of drugs, having the ability to block the neurotransmission of dopamine receptors in the central nervous system, have been developed. Examples of said drugs are phenothiazine-type compounds such as Chlorpromazine; butyrophenone-type compounds such as Haloperidol; and benzamide-type

-2-

compounds such as Sulpiride. These known drugs are now used widely for the purpose of improving so-called positive symptoms in the acute period of schizophrenia such as hallucinations, delusions and excitations and the like.

5

However, many of these drugs are considered as not effective for improving the so-called negative symptoms, which are observed in the chronic period of schizophrenia such as apathy, emotional depression, hypopsychosis and the like. In addition
10 to the above, these drugs give severe side-effects such as akathisia, dystonia, Parkinsonism dyskinesia and late (tardive) dyskinesia and the like, which are caused by blocking the neurotransmission of dopamine receptors in the striatum. Furthermore, other side-effects such as hyperprolactinemia are seen with these drugs. [Cf. G. M. Simpson, E. H. Pi,
15 and J. J. Sramek, Jr.: Drugs, Vol. 21, pp. 138 (1981).]

Under these circumstances, development of drugs for treating schizophrenia, having safety and clinical effectiveness
20 against both positive and negative symptoms, is still needed. In particular, so-called "dopamine stabilizers" are thought to be valuable drugs against both positive and negative symptoms of schizophrenia (see Carlsson et al. above).

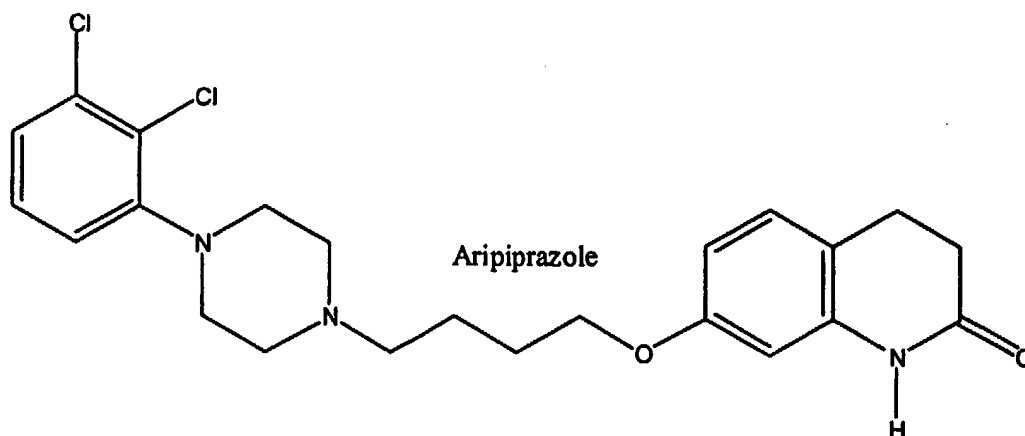
25 Drugs known in the prior art for treating schizophrenia induce a number of side-effects. Example of such side-effects are those induced by phenothiazine-type drugs, i.e. the orthostatic hypotension and hypersedation on the basis of strong alpha-blocking activity; and in the case of drugs hav-
30 ing strong activity for blocking neurotransmission of dopaminergic receptor, the side-effects are so-called extrapyramidal side-effects such as catalepsy, akathisia, dystonia and the like caused by blocking the neurotransmission of dopamine receptors in the striatum.

35

A number of carbostyryl derivatives for therapeutical use has also been disclosed. Among carbostyryl derivatives known in prior art are those disclosed in: EP-A-0367141, Publication

date: 1990-05-09, Applicant(s): OTSUKA PHARMA CO LTD (JP), Priority Number(s): JP19880276953 19881031. The "3rd generation anti-psychotic" Aripiprazole emanates from that patent application.

5



U. S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patents Nos. 2,911,108, 1,912,105 and 2,953,723; Japanese Patent Kokai (Laid-open) Nos. 54-130,587 (1979), 55-127,371, (1980) and 62-149,664 (1987) are having chemical structural formulas related to Aripiprazole.

Furthermore, carbostyryl derivatives disclosed in US-A-4,234,585 and EP-A-226,441 have chemical structural formula similar to that of Aripiprazole.

In addition to the above, the carbostyryl derivatives disclosed in US-A-4,234,584 have chemical structural formula similar to that of Aripiprazole and also have pharmacological activities similar to those shown by Aripiprazole.

Carbostyryl derivatives are also disclosed in Australian Patent No. 50252/85, Japanese Patent Kokai (Laid-open) Nos. 58-43952 (1983), 56-49359 (1981), 56-49360 (1981) and 56-49361 (1981).

It is an object of the present invention to provide a novel thio-carbostyryl derivative, its N-oxides and the N-oxides of

Aripiprazole and salts thereof, which are devoid of the side-effects induced by known drugs for treating schizophrenia.

5 A further object of the present invention is to provide processes for preparing said thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole and salts thereof.

10 A still further object of the present invention is to provide a pharmaceutical composition for treating schizophrenia, Huntington's disease and dyskinesias in Parkinson's disease.

15 A still further object of the present invention is to provide a pharmaceutical composition for treating erectile dysfunction.

Summary of the invention

20 According to the present invention there is provided a novel thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole and salts thereof, which were surprisingly found to exhibit strong activity for influencing neurotransmission of dopamine receptors and being devoid of the side-effects induced by known drugs for treating schizophrenia, said derivative being 7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione, its N-oxides and
25 the N-oxides of Aripiprazole, having the Formulas 1-7:

Formula 1: thio-ari

Formula 2: thio-ari n-ox (basic N)

30 Formula 3: thio-ari n-ox (anilinic N)

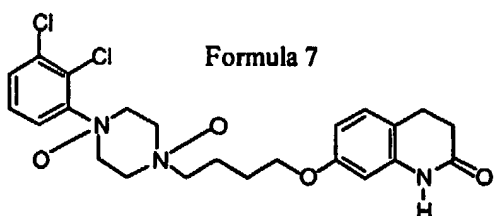
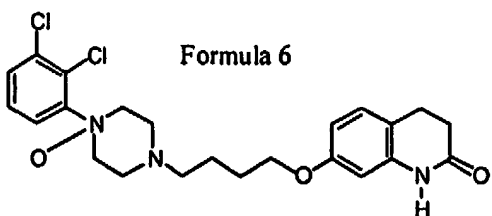
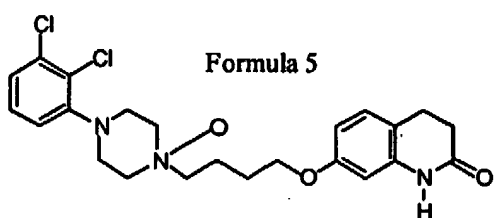
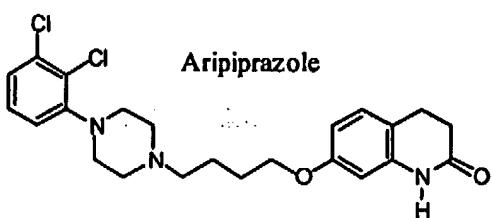
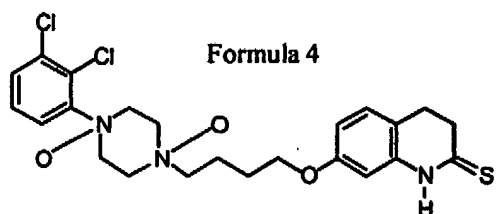
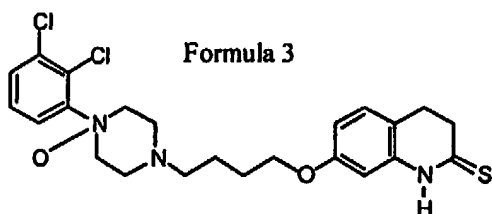
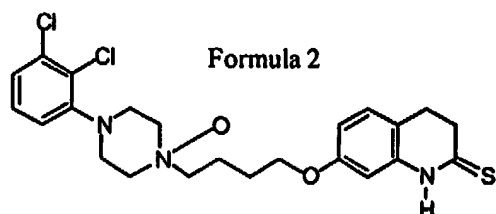
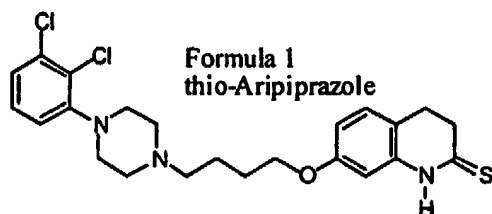
Formula 4: thio-ari di-n-ox

Formula 5: ari n-ox (basic N)

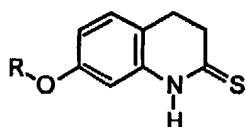
Formula 6: ari n-ox (anilinic N)

Formula 7: ari di-n-ox

**CHEMICAL STRUCTURES OF ARIPIPAZOLE AND THE NEW
COMPOUNDS OF THE PRESENT INVENTION**



Even though the chemical structures of the thio-carbostyryl derivative of the present invention and Aripiprazole (see above) and other carbostyryl derivatives of the prior art are very similar, their corresponding pharmacological profiles are distinct. In addition, the thio-carbostyryl group of Formula 8 below is not part of any known chemical structure to date:



Formula 8

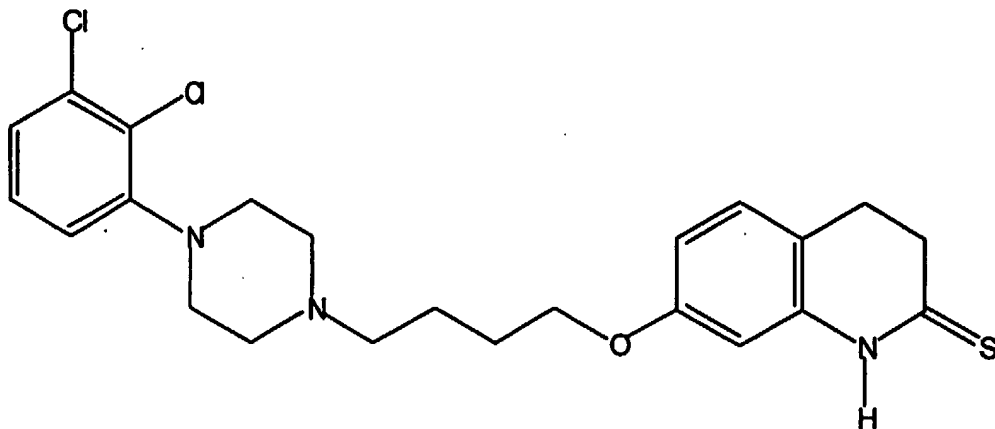
The present invention also provides a pharmaceutical composition comprising said thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole or a physiologically acceptable salt thereof as an active ingredient optionally together with at least one member selected from the group consisting of pharmaceutically acceptable carriers, diluents and excipients.

The present invention further provides processes for the preparation of the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole of the present invention and salts thereof.

Further, the present invention provides the use of the thio-carbo-styryl derivative, its N-oxides and the N-oxides of Aripiprazole of the present invention for the preparation of a pharmaceutical formulation for the treatment of central nervous system (CNS) disorders in mammals including man.

Detailed description of the preferred embodiments

According to one aspect of the present invention there is provided the novel thio-carbostyryl derivative 7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione represented by the formula (1):



, its N-oxides and the N-oxides of Aripiprazole and the physiologically acceptable salts thereof (see Formulas 1-7 above).

5 The thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole and salts thereof, represented by the Formulas 1-7, possess strong activity for inhibiting the neurotransmission at dopamine receptors. Surprisingly we found that the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole of Formulas 1-7 display a favorable
10 atypical anti-psychotic pharmacological profile. The thio-carbostyryl derivative of Formula 1 surprisingly displays a receptor binding selectivity profile, which is more favorable than that of Aripiprazole.

15

The thio-carbostyryl derivative of Formula 1 (thio-Aripiprazole) was, surprisingly, shown to form Aripiprazole in vivo after the administration of 100 $\mu\text{mol/kg}$ i.p. In the brain sample there was more Aripiprazole than thio-Aripiprazole. This was also true, at lower absolute concentrations, in the blood sample. This means that thio-Aripiprazole has both pharmacological effects in its own and it also forms Aripiprazole via bio-activation. Thus, thio-Aripiprazole works both as a drug and as a pro-drug. These features of the
20 Formula 1 compound of the present invention (thio-
25

Aripiprazole) renders its unique properties as an atypical antipsychotic agent.

The thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole represented by the Formulas 1-7 of the present invention can easily be converted into their acid-addition salts by reacting them with a pharmaceutically acceptable acid. Examples of such acids include inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid and the like. A thio-carbostyryl derivative, represented by the Formula 1 of the present invention, which has an acidic -NH- thio-amide group, can easily be converted into its salts by reacting with basic compounds. Examples of such basic compounds include sodium-amide and LDA.

According to another aspect the present invention provides a pharmaceutical composition comprising said thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole or a physiologically acceptable salt thereof as an active ingredient optionally together with at least one member selected from the group consisting of carriers, diluents and excipients.

Thus, in accordance with this aspect of the invention the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole represented by the Formulas 1-7 can be used in the form of usual pharmaceutical compositions, which are prepared by using at least one member selected from the group consisting of carriers, diluents and excipients such as fillers, bulking agents, binders, wetting agents, disintegrating agents, surface active agents, lubricants and the like. As to the pharmaceutical compositions, various types of administration unit forms can be selected depending on the therapeutic purposes, and the examples of pharmaceutical compositions are tablets, pills, powders, liquids, suspensions, emulsions,

granules, capsules, suppositories, injection preparations (solutions and suspensions), bio-degradable polymers and the like. For the purpose of shaping the pharmaceutical composition in the form of tablets, any excipients which are known and used widely in this field can also be used, for example carriers such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and the like; binders such as water, ethanol, propanol, simple sirup, glucose solutions, starch solutions, gelatin solutions, carboxymethyl cellulose, she-lac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone and the like; disintegrating agents such as dried starch, sodium alginate, agar powder, laminaria powder, sodium hydrogen carbonate, calcium carbonate, fatty acid esters of polyoxyethylene sorbitan, sodium laurylsulfate, monoglyceride of stearic acid, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, coconut butter, hydrogenated oils; absorption accelerators such as quaternary ammonium base, sodium laurylsulfate and the like; wetting agents such as glycerin, starch and the like; adsorbing agents such as starch, lactose, kaolin, bentonite, colloidal silicic acid and the like; and lubricants such as purified talc, stearates, boric acid powder, polyethylene glycol and the like. If tablets are desired, they can be further coated with the usual coating materials to make the tablets as sugar coated tablets, gelatin film coated tablets, tablets coated with enteric coatings, tablets coated with films, double layered tablets and multi-layered tablets.

For the purpose of shaping the pharmaceutical composition in the form of pills, any excipients which are known and widely used in this field can also be used, for example, carriers such as lactose, starch, coconut butter, hardened vegetable oils, kaolin, talc and the like; binders such as gum arabi powder, tragacanth gum powder, gelatin, ethanol and the like; disintegrating agents such as agar, laminaria and the like.

For the purpose of shaping the pharmaceutical composition in the form of suppositories, any excipients which are known and widely used in this field can also be used, for example polyethylene glycols, coconut butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthesized glycerides and the like.

For the purpose of shaping the pharmaceutical composition in the form of injection preparations, solutions and suspensions are sterilized and are preferably made isotonic to blood. In making injection preparations, any carriers which are usually used in this field can also be used, for example, water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, fatty acid esters of polyoxyethylene sorbitan. In these instances, adequate amounts of sodium chloride, glucose or glycerin can be added to the desired injection preparations to make them isotonic. Furthermore, usual dissolving agents, buffer agents, analgesic agents may be added. Yet further, if necessary, coloring agents, preservatives, perfumes, seasoning agents, sweetening agents and other medicines may also be added to the desired preparations during the treatment of schizophrenia.

The amount of the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole of Formulas 1-7 or salt thereof to be contained in a pharmaceutical composition for treating schizophrenia according to the present invention is not specifically restricted and can suitably be selected from a wide range, usually it is contained 1 to 70%, preferably 1 to 30% by weight of the whole composition.

Administration methods of a pharmaceutical composition for treating schizophrenia of the present invention are not specifically restricted, and the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole of the present invention can be administered in various forms of preparations depending on the age of the patient, distinction of sex, other conditions, as well as conditions of the symptoms.

For example, tablets, pills, solutions, suspensions, emul-
sions, granules and capsules are orally administered; and in-
jection preparations are administered singly or mixed with
injection transfusions such as glucose solutions and amino
5 acid solutions intravenously; and if necessary, the injection
preparations are administered singly intramuscularly, in-
tracutaneously, subcutaneously or intraperitoneally. Supposi-
tories are administered into the rectum. Bio-degradable poly-
mers are implanted under the skin or used orally.

10

The dosage of a pharmaceutical composition for treating
schizophrenia according to the present invention is suitably
selected according to the method of use, the age of the pa-
tient, distinction of sex, other conditions, as well as con-
15 ditions of the symptoms, usually about 0.1 to 10 mg/kg of the
body weight/day of the thio-carbostyryl derivative, its N-
oxides and the N-oxides of Aripiprazole of Formulas 1-7 as
the active ingredient may be administered. Usually, 1 to 200
mg of the active ingredient may be contained in an admini-
20 stration unit form.

According to a further aspect of the invention there is pro-
vided a process for the preparation of the thio-carbostyryl
derivative of the present invention which process comprises
25 reacting aripiprazole with Lawesson's reagent (2,4-bis(4-
methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-di-sulfide)
or phosphorous pentasulphide at appropriate temperatures.

The principles of this reaction are known per se from litera-
30 ture (vide e.g. Bull. Soc. Chim. Belg. 87, 223, 229, 299, 525
(1978)).

According to this aspect there is also provided a process for
the preparation of N-oxides of the thio-carbostyryl deriva-
35 tive of Formula 1 or of aripiprazole, which process comprises
reacting the thio-carbostyryl derivative of Formula 1 and
aripiprazole, respectively, with m-chloroperbenzoic acid.

In accordance with another aspect of the present invention there is provided the use of the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole of the present invention for the manufacture of a pharmaceutical composition
5 for the treatment of central nervous system CNS disorders in mammals, including man.

According to one embodiment of this aspect of the invention said pharmaceutical composition is suited for treating dopa-
10 mine receptor related central nervous neuro-psychiatric diseases and/or for treating circulatory disorders. Important examples of such dopamine receptor related central nervous neuro-psychiatric diseases and circulatory disorders are schizophrenia; dyskinesias by Parkinson's disease, e.g. dy-
15 skinesias caused by long-term L-dopa; and Huntington's disease.

According to another embodiment of this aspect of the invention said pharmaceutical composition is suited for treating
20 drug abuse, in particular alcohol and/or cocaine abuse.

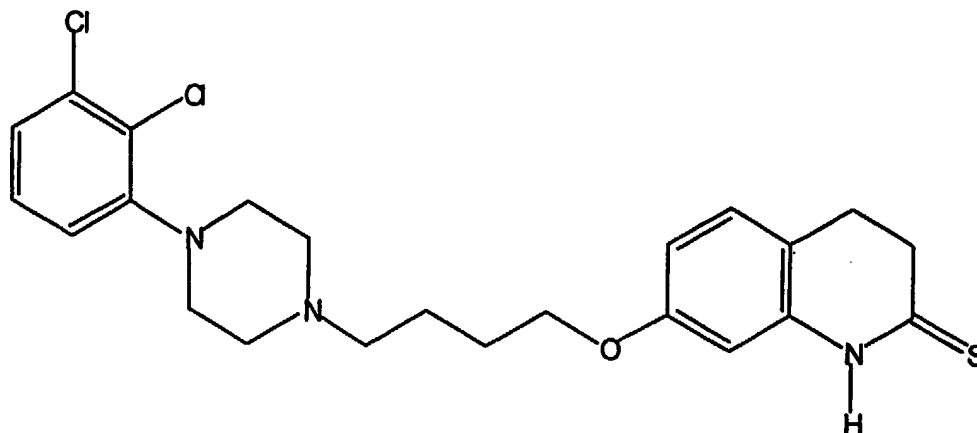
According to a further embodiment of this aspect said pharmaceutical composition is suited for the treatment of erectile
25 dysfunction.

According to a still further aspect of the present invention there is provided a process for the preparation of a pharmaceutical composition, characterized in that the compounds of
30 Formulas 1 according to the invention or a physiologically acceptable salt thereof is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

The invention will now be further described by means of a number of examples which are not to be construed as limiting
35 the present invention.

Example 1

Aripiprazole (OPC-14597, CAS RN 129722-12-9; 1.00 g, 2.23 mmol) was dissolved in toluene (25 mL). To this solution was added Lawesson's reagent (1.08 g, 2.68 mmol) and the reaction mixture was refluxed for one hour. TLC was best run on silica pretreated with ammonia (NH₃ (g)) and with EtOAc as eluent. The solvent was evaporated and the orange residue was dissolved in methylene chloride (50 mL) and washed with 10 % Na₂CO₃ (2 x 15 mL). The organic layer was dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure, leaving 1.4 g of crude product. This product was first dissolved in methylene chloride and applied on top of a silica column, eluting with a mixture of methylene chloride and methanol (20:1). By this procedure, two products were seen on TLC, eluting with a mixture of methylene chloride and methanol (10:1). The fractions containing the two products were pooled and the solvent was evaporated under reduced pressure, leaving about 1 g of product mixture. To this mixture was sequentially added ethanol (50 mL-40 mL-20 mL) and the mixture was heated to reflux, the hot solvent was decanted and the next portion of ethanol was added. Crystals precipitated as crops 1-3, of which only crop 1 contained the pure product. Now switching to TLC in EtOAc on glass plates pretreated with ammonia, it was obvious that there was very little of the wanted product in crops 2 and 3, while their corresponding mother liquors contained much of the product. The mother liquors from crops 1-3 were pooled and the solvent was evaporated under reduced pressure, leaving about 0.5 g, which was dissolved in methylene chloride and applied on top of an ammonia pretreated silica column, and eluting with EtOAc. In fractions 1-5 about 20 mL were collected and the bulk of the pure product appeared in fractions 2-4. These fractions were pooled and the solvent was evaporated under reduced pressure, yielding 300 mg, which was pooled with crop 1 (400 mg) and was recrystallized in about 5 mL refluxing 100% EtOH. Crystals were filtered and dried, yielding white to light yellow crystals (600 mg) melting at 139-140°C. API MS (SCIEX) showed $M + 1 = 464$ and an isotope pattern of 2 Cl atoms.



7-{4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione

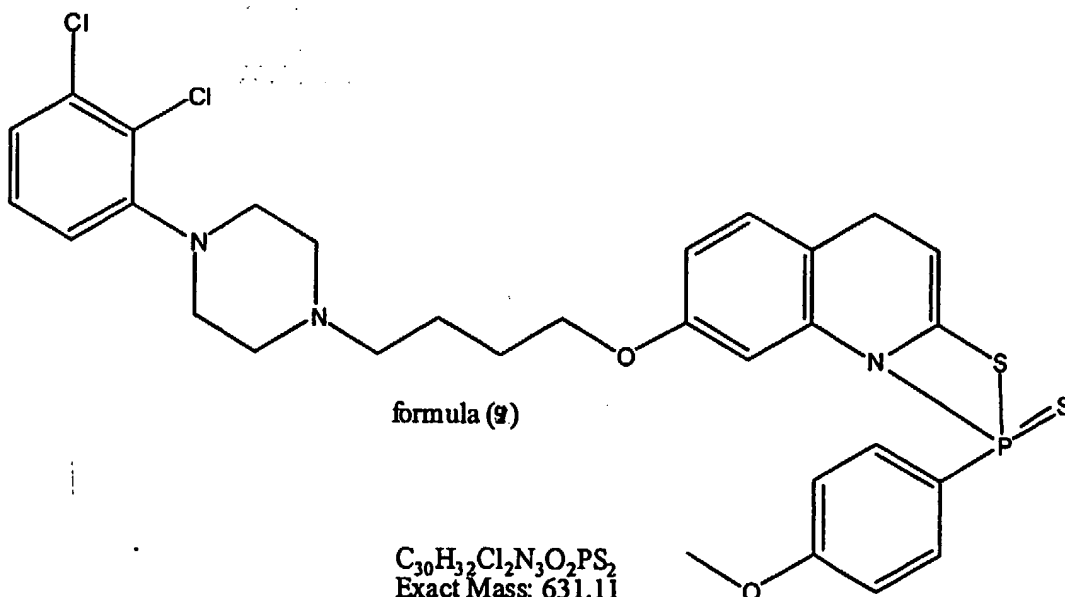
C₂₃H₂₇Cl₂N₃OS

Exact Mass: 463.13

Mol. Wt.: 464.45

C, 59.48; H, 5.86; Cl, 15.27; N, 9.05; O, 3.44; S, 6.90

In order to find out which byproduct had been formed, crystals from crop 3 were dissolved in acetic acid (these crystals do neither dissolve in methylene chloride nor in ethanol), a droplet was taken out and dissolved in methanol and perfused into the ion spray SCIEX MS/MS mass spectrometer. The M+1 peak at 632, containing two chloro atoms, is likely to be:



formula (9)

C₃₀H₃₂Cl₂N₃O₂PS₂

Exact Mass: 631.11

Mol. Wt.: 632.61

C, 56.96; H, 5.10; Cl, 11.21; N, 6.64; O, 5.06; P, 4.90; S, 10.14

Example 2

Conversion of Aripiprazole (10 mg) to thio-Aripiprazole with Lawesson's reagent (0.6 equivalents) in toluene (1 mL) at 100°C for 30 min. 10% NaHCO₃ (1 mL) was added and the covered vial was vortexed and the organic layer was diluted with EtOAc (1 mL) before pipetting it off, applying it on top of a Pasteur pipette filled with NH₃ (g) pre-treated SiO₂. Eluting with EtOAc (0.5 mL/fraction) gave the product in fractions 7-12. Fractions 8-10 were pooled, the solvent was evaporated and the crystalline remains were recrystallized from refluxing 100% EtOH, yielding 4.9 mg white crystals melting at 139-140°C.

Example 3**Synthesis of the N-oxides of Aripiprazole**

Synthesis of aripiprazole-N(basic N)-mono-oxide (formula 5)

Aripiprazole (Mw 447, 25 mg, 56 µmol) was dissolved in about 1 mL methylene chloride. To this solution was added (dropwise at room temperature) m-chloroperbenzoic acid (MCPBA, Mw 173, 19 mg, 112 µmol). A TLC (alumina eluting with methylene chloride/methanol 20/1) was run after about one hour and showed no starting material and a new spot, with a R_f value of about 0.4. The same eluent was used when chromatographing in a Pasteur pipette (alumina). About 1 mL fractions were collected and the product was isolated and the solvents were removed by evaporation, leaving a solid foam (27 mg), which was identified by API MS (M+1 = 464, showing an isotope relation indicating two Cl atoms).

Example 4**Synthesis of aripiprazole-N₂,N₄a-di-oxide**

Aripiprazole (Mw 447, 100 mg, 224 µmol) was dissolved in about 5 mL methylene chloride. To this solution was added (at room temperature) m-chloroperbenzoic acid (MCPBA, Mw 173, 200 mg, 1160 µmol). A TLC (alumina eluting with methylene chloride/methanol 20/1) was run after about one hour and showed no starting

material and a new spot, with a Rf value of about 0.2. The same eluent was used when chromatographing in a Pasteur pipette (alumina). About 1 mL fractions were collected and the product was isolated and the solvents were removed by evaporation, leaving a solid (50 mg), which was identified by API MS ($M+1 = 480$, showing an isotope relation indicating two Cl atoms).

Example 5

Synthesis of the N-oxides of thio-Aripiprazole (formula 2)

10 An analytical sample of about 1 mg of thio-Aripiprazole (base) was dissolved in 0.5 mL of methylene chloride and a few drops from a Pasteur pipette of a solution of about 10 mg MCPBA in 1 mL methylene chloride were added at room temperature. After five minutes TLC was run on alumina (Al_2O_3) eluting with methylene chloride: methanol (20:1). This TLC showed thio-Aripiprazole at $R_t = 0.97$, a new
15 spot at $R_t = 0.86$ (likely to be mono-N-oxide at the basic nitrogen atom of the piperazine ring) and another new spot at $R_t = 0.46$ (likely to be di-N-oxide, i.e. both nitrogen atoms of the piperazine ring have been oxidized). TLC was checked after night in room temperature but showed no further reaction, which indicates that the oxidation had stopped halfway due to the addition of too little MCPBA to
20 convert all the starting material to N-oxidized products.

In order to identify the spots, HPLC/MS/MS was performed as described elsewhere in this patent application with a reversed phase column, eluting with a CH_3CN /water gradient running from 15% to 95% CH_3CN . The following peaks
25 were registered (all showing the isotope Relationship of two Cl atoms):

Retention time = 11.2 minutes (small amount of Aripiprazole formed; $M + 1 = 448$; 7.7 e5 cps; MS/MS 448/285 is Aripiprazole/di-Cl-phpip- $CH_2CH_2CH_2CH_2$)

30 Retention time = 11.3 minutes (thio-Aripiprazole-N-oxide; $M + 1 = 480$; 4.0e6 cps; MS/MS 480/243 is thio-Aripiprazole-N-oxide/di-Cl-phpip- CH_2)

Retention time = 11.5 minutes (thio-Aripiprazole-di-N-oxide; $M + 1 = 496$; 3.0e6 cps; MS/MS 496/243 is thio-Aripiprazole-di-N-oxide/di-Cl-phpip- CH_2)

35 Retention time = 12.4 minutes (thio-Aripiprazole; $M + 1 = 464$; 4.5e6 cps; MS/MS 464/285 is thio-Aripiprazole/di-Cl-phpip- $CH_2CH_2CH_2CH_2$)

Example 6**Pharmacokinetic experiment with Aripiprazole and thio-Aripiprazole****5 Analysis of drug levels in brain and blood**

Two rats were treated with either Aripiprazole (100 $\mu\text{mol/kg}$ i.p.) or thio-Aripiprazole (100 $\mu\text{mol/kg}$ i.p.). After 2 hours, the animals were killed and blood was collected via heart
10 punktion. The brains were removed and homogenized. The biological sample were centrifuged at 10,000 r.p.m. and the supernatant was transferred to test tubes with a pipett and were stored until further workup and analysis. Samples were spiked with the standard mono-pivaloyl-apomorphine.

15 Proteins were precipitated with CH_3CN /water (60 %) and centrifugation and decanting gave a clear solution, which was concentrated by blowing nitrogen gas at room temperature. The remaining material was re-dissolved in the HPLC starting eluent CH_3CN /water (15 %) and was analyzed by HPLC/MS/MS, utilizing a gradient system and a SCIEX MS/MS mass spectrometer.
20

Results**25 Rat with thio-aripiperazole injected:**

Brain: 160 nM thio-aripiprazole, 1.4 μM Aripiprazole

Blood: 60 nM thio-aripiprazole, 160 nM Aripiprazole

Rat with aripiperazol injected:

30 Brain: 4.7 μM Aripiprazole

Blood: 660 nM Aripiprazole

(no thio-aripiperazole was detected in these samples)

The calibration curve was not linear, and the standard also
35 varied between the samples. The concentrations must therefore not be regarded as absolute values.

Example 7**Pharmacokinetic experiment with Aripiprazole-mono-N-oxide, a comparison with thio-Aripiprazole**

5 Aripiprazole-mono-N-oxide (100 μ mol/kg) was difficult to dissolve (10 microliters acetic acid, water, PEG and DMSO, totally about 1 mL) and was administered orally to a rat weighing about 300 g. No dramatic behavioural effects were seen, but the rat showed no signs of catalepsy behavior. After two hours, the rat was anesthetized (isoflurane) and was killed by heart puncture. Blood was collected and the brain was taken out to be homogenized in 60 percent
10 CH₃CN/water, containing also small amounts of HCOOH and HSCH₂CH₂OH.

About half of the amount of plasma and brain extract was evaporated (normally this is not 4 mL out of 8 mL but rather 0.5 mL. Thus, to compare the data from a
15 former experiment we have to consider a factor of eight to compensate for this difference).

HPLC/MS/MS

20 The usual CH₃CN/ water gradient system was used without an internal standard.

Aripiprazole-mono-N-oxide has a retention time = 11.31 minutes (464/243)

Aripiprazole has a retention time = 11.14 (448/285)

25

Comparison table:

Drug administered	ARI-N-OX cps		ARI cps	
	blood	brain	blood	brain
THIO-ARI	-	-	28,600	2,920
ARI-N-OX	47,400	2,070	195,000	126,000
(1/8	5,925	259	24,375	15,750)

35

Surprisingly, Aripiprazole is generated from both Aripiprazole-mono-N-oxide and from thio-Aripiprazole.

Example 8**Pharmaceutical preparation**

By using usual procedures tablets each weighing 200 mg were prepared from the following ingredients in the proportions indicated

Ingredient	Amount [mg]
7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione	5 mg
10 Starch	132 mg
Magnesium stearate	18 mg
Lactose	45 mg
Total	200 mg

15 **Example 9**

Pharmaceutical preparation

An injection solution was prepared from the following components:

Component	Amount
7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione	500 mg
Polyethylene glycol (molecular weight: 4,000)	0,3 g
25 Sodium chloride	0,9 g
Polyoxyethylene sorbitan monooleate	0,4 g
Sodium metabisulfite	0,1 g
Methyl p-hydroxybenzoate	0,18 g
Propyl p-hydroxybenzoate	0,02 g
30 Distilled water for injection	100 ml

The above-mentioned methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sodium metabisulfite and sodium chloride were dissolved in distilled water for injection at 80°C with stirring. The resulting solution was cooled to 40°C, then 7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione, polyethylene glycol and polyoxyethylene sorbitan monooleate were dissolved in the above-

mentioned solution in this order, then the predetermined volume of the injection solution was adjusted by adding the distilled water for injection, and was sterilized by filtration by using a suitable filter paper, then 1 ml each of the desired injection solution was filled in an ampoule.

Pharmacological Tests

Contralateral turning in 6-OH-DA lesioned rats

The compound of the present invention may be evaluated in rats unilaterally lesioned with 6-hydroxydopamine (6-OH-DA) (Ungerstedt and Arbuthnott, Brain Res. 1970, 24, 485-493). In this model, the DA neurons of one side (left or right) of the nigrostriatal DA system are selectively and completely degenerated by intracebral injection of the neurotoxin 6-OH-DA. This causes a postsynaptic supersensitivity to develop on the lesioned side. Upon systemic administration of a DA agonist, the rat will start to turn contralaterally, i.e. towards the non-lesioned side. The evoked turning behavior is a measure of the DA (D1 and/or D2) agonist properties of a compound and can be inhibited by DA partial agonists and antagonists.

a) Anti-apomorphine activity in 6-OH-DA lesioned rats (the Ungerstedt model)

Haloperidol was administered subcutaneously (s.c.) to the rats at a dose of 1 mg/kg body weight. Apomorphine was administered subcutaneously to the rats in doses of 0.05, 0.1 and 0.25 mg/kg body weight ("Apomorphine 0.05", etc. in the Tables below). Aripiprazol and 7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione ("thio-aripiprazole") were each administered intraperitoneally (i.p.) at a dose of 10 mg/kg.

The results are given in Tables 1 to 3 below.

Table 1

Substance tested	Accumulated full rotations over the period of activity in rat number						
	61	63	64	53	54	55	56
Haloperidole	2	2	0	5	6	1	3
Apomorphine 0.05	3	2	2	10	84	7	0
Apomorphine 0.1	30	1	4	71	44	5	113
Apomorphine 0.25	6	0	39	369	474	307	223

Table 2

Substance tested	Accumulated full rotations over the period of activity in rat number							
	69	73	74	75	61	63	64	66
Aripiprazole	0	256	142	5	3	5	3	47
Apomorphine 0.05	512	396	508	154	44	5	316	602
Apomorphine 0.1	687	336	467	294	14	14	290	595
Apomorphine 0.25	841	194	360	180	472	328	286	388

5 Table 3

Substance tested	Accumulated full rotations over the period of activity in rat number							
	53	54	56	57	61	63	64	65
Thio-aripiprazole	4	6	6	3	0	1	7	0
Apomorphine 0,05	510	367	309	470	41	11	35	382
Apomorphine 0,1	687	250	390	532	168	28	106	627
Apomorphine 0,25	999	409	500	724	498	826	381	383

b) Catalepsy measurements

10 Catalepsy was observed by placing the animals on an inclined grid 60 degrees for a maximum of 2.25 min, in a lit room. The animals were allowed 30 s of adaptation on the grid, at every measuring occasion, before the observation (stop watch) was started. The catalepsy was expressed as a score from 0 to 5, according to the time. square root transformation the rat re-
 15 mained immobile. min : 0 s 0.00-0.08; 1 s 0.09-0.35; 2 s 0.36-0.80; 3 s 0.81-1.42; 4 s 1.43-2.24; 5 s)2.25 min, i.e., if the rat remained immobile for 0.08 min, it was scored as

0, etc. (see Ahlenius and Hillegaart, 1986, Pharmacol. Biochem. Behav. 24, 1409-1415.)

No catalepsy was registered for neither Aripiprazole nor
5 thio-Aripiprazole (formula 1) at the i.p. dose 100 μ mol/kg.

Microdialysis in rat striatum

10 Male Wistar rats (from Harlan, Zeist, The Netherlands) weighing 280-320 g were used, and housed as described for the locomotor activity experiments. On line brain microdialysis in freely moving animals was essentially performed as described previously (Westerink, Trends in Anal. Chem. 1992, 11, 176-
15 182). Briefly, rats were anesthetized with choral hydrate (400 mg/kg ip) and 10% lidocaine locally applied. The rats were then mounted into a stereotaxic frame (Kopf). The incisor bar was placed in position so that the skull was held in a horizontal position. The skull was exposed and burr holes
20 were drilled. An Y-shaped cannula was used for the experiments, with an exposed tip length of 3 mm. The dialysis tube (ID: 0.22 mm; OD: 0.31 mm) was prepared from polyacrylonitrile methalys sulfonate copolymer (AN 69, Hospal, Bologna, Italy). The dialysis membrane was implanted in the Striatum
25 with coordinates which were calculated relative to bregma: A + 1, L 3, D 6 according to the brain atlas of Paxinos and Watson (1982). The dura was removed with a sharp needle. Two anchor screws were positioned in different bone plates nearby. Before insertion into the brain the dialysis probes
30 were perfused with successively ultra pure water, methanol, ultra pure water and Ringer solution (1.2 mM Ca^{2+}). The dialysis probe was positioned in the burr hole under stereotaxic guidance. The probe was cemented in this position with phosphatine dental cement (Associated dental products LTD,
35 Kemdent Works, Purdon, Swinden, Wiltshire SN 5 9 HT).

The experiments were performed in conscious rats 17-56 h after implantation of the cannula. The striatum was perfused

with a Ringer solution (147 mM NaCl, 4 mM KCl, 1.2 mM CaCl₂, 1.1 mM MgCl₂) at 2 l/min (CMA/102 microdialysis pump). After the experiments the rats were sacrificed and the brains were removed. After removal the brains were kept in 4 % paraformaldehyde solution until they were sectioned to control the location of the dialysis probes.

Dopamine, dihydroxyphenylacetic acid (DOPAC) and 5-HIAA were quantitated by HPLC with electrochemical detection. An HPLC pump (LKB, Pharmacia) was used in conjugation with an EC-detector (Antec, Leiden) working at 625 mV versus Ag/AgCl reference electrode. The analytical column was a Supelco Supelcosil LC-18 Column (15 cm, 4.6 mm, 3 µm). The mobile phase consisted of a mixture of 4.1 g/l sodium acetate (Merck), 85 mg/l octane sulphonic acid (Aldrich), 50 mg/l EDTA (Merck), 8.5 % methanol (Labscan) and ultra pure water (pH=4.1 with glacial acetic acid).

Statistics: The microdialysis data were analyzed using Friedman Repeated Measures Analysis of Variance on Ranks with as post-hoc test Dunnetts Method.

Microdialysis results

Aripiprazole and 7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione ("thio-aripiprazole") (10 mg/kg i.p. of both compounds) were dissolved in 0.1 mL EtOH, 0.3 mL PEG and 0.6 mL water and were injected i.p. in the test animals.

During this experiment there was a maximum increase in DOPAC of from 160 % to 200 % relative to the control in case of the dose of 10 mg/kg i.p. of aripiprazole and a maximum increase in DOPAC of from 160 % to 210 % relative to the control in case of the dose of 10 mg/kg i.p. of thio-aripiprazole.

Behavioral experiment with Thio-Aripiprazole.

Two rats were first injected subcutaneously with 1 mg/kg of the test compound. Weak dopaminergic stimulation was observed, including penile licking. 15 minutes later, 10 mg/kg subcutaneously was injected. The animals were calm. However, after about 10 minutes both animals intensely were grooming their penis (penile grooming). This behavior was more intense than that seen after apomorphine itself.

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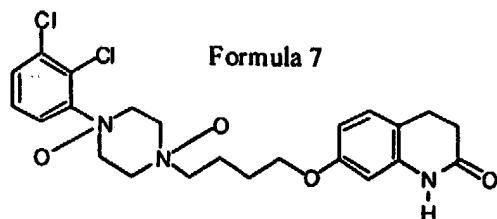
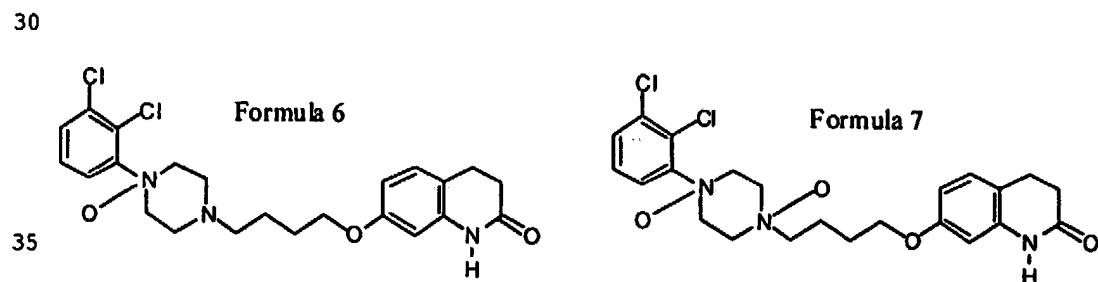
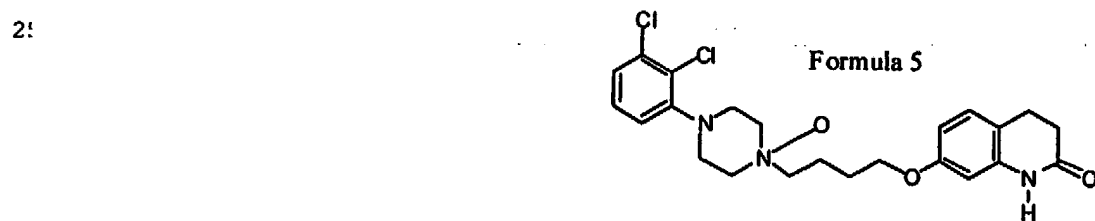
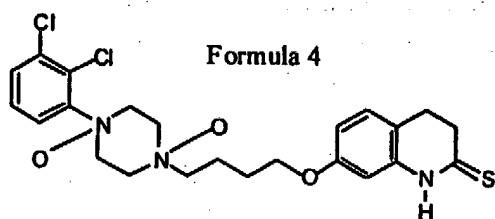
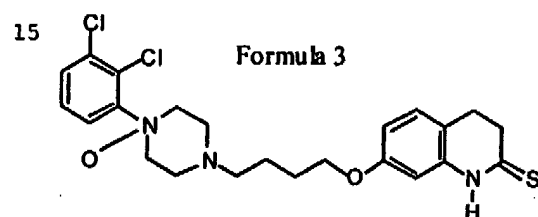
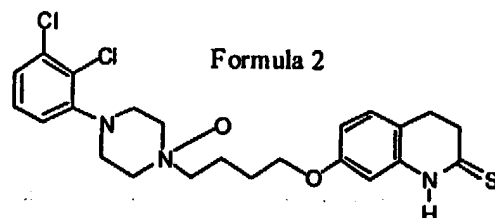
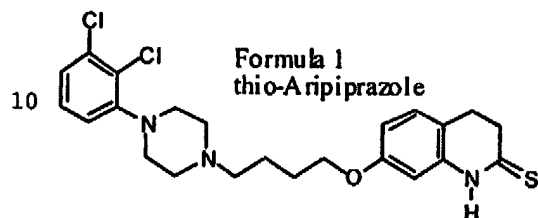
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CLAIMS

1. The thio-carbostyryl derivative 7-[4-[4-(2,3-dichloro-
phenyl)-piperazin-1-yl]-butoxy]-3,4-dihydro-1H-quinoline-2-
thione, its N-oxides and the N-oxides of Aripiprazole, repre-
sented by Formulas 1-7:



and their salts.

2. The thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole according to claim 1, wherein the salts thereof are physiologically acceptable acid addition salts with inorganic or organic acids.

5

3. Pharmaceutical composition comprising as an active ingredient the thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole of claim 1 or a physiologically acceptable salt thereof optionally together with at least one member selected from the group consisting of carriers, diluents and excipients.

10

4. Pharmaceutical composition according to claim 3, wherein said physiologically acceptable salt is an acid addition salt.

15

5. Process for the preparation of a thio-carbostyryl derivative as identified in claim 1, which process comprises reacting aripiprazole with Lawesson's reagent or phosphorous pentasulphide.

20

6. Process for the preparation of N-oxides of the thio-carbostyryl derivative of Formula 1 or of aripiprazole, which process comprises reacting the thio-carbostyryl derivative of Formula 1 and aripiprazole, respectively, with m-chloroperbenzoic acid.

25

7. Use of a thio-carbostyryl derivative, its N-oxides and the N-oxides of Aripiprazole as identified in claim 1, or a physiologically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of central nervous system (CNS) disorders in mammals, including man.

30

8. Use according to claim 7, wherein the pharmaceutical composition is for the treatment of dopamine receptor related central nervous neuro-psychiatric diseases and/or for treating circulatory disorders.

35

9. Use according to claim 7, wherein the pharmaceutical composition is for the treatment of schizophrenia.
10. Use according to claim 7, wherein the pharmaceutical composition is for the treatment of dyskinesias by Parkinson's disease.
11. Use according to claim 7, wherein the pharmaceutical composition is for the treatment of Huntington's disease.
12. Use according to claim 7, wherein the pharmaceutical composition is for the treatment of drug abuse.
13. Use according to claim 7, wherein the pharmaceutical composition is for the treatment of erectile dysfunction.
14. Process for the preparation of a pharmaceutical composition characterized in that 7-{4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy}-3,4-dihydro-1H-quinoline-2-thione, its N-oxides and the N-oxides of Aripiprazole or a physiologically acceptable salt thereof is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

L Number	Hits	Search Text	DB	Time stamp
1	0	aripiprazole and cyclodextrin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:40
2	2	aripiprazole and cyclodextrin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:02
3	3	carbostyrl? and cyclodextrin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:22
4	0	(carbostyrl? and cyclodextrin) and (sulfobutyl with cyclodextrin)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:22
5	2	(carbostyrl? and cyclodextrin) and (tartaric or citric or hydrochloric or acetic or maleic or malic or sulfuric or toluenesulfonic)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:25
6	1	((carbostyrl? and cyclodextrin) and (tartaric or citric or hydrochloric or acetic or maleic or malic or sulfuric or toluenesulfonic)) and carbostyrl	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:37
7	0	(phenylpiperazino adj butoxyl adj carboxtyrl) or (phenyl adj piperazino adj butoxyl adj carboxtyrl)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:38
8	0	aripiprazole adj complex	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:41
9	0	aripiprazole with complex	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/24 12:41
-	2	"5506216"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/10 15:31
-	0	methyl-cyclodextrin with (formula or structure)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/10 15:04
-	2	(methyl adj cyclodextrin) with (formula or structure)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/10 15:05

-	15	myrosinase.tl.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/10 15:39
-	59	myrosinase.ab.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/10 15:39
-	35	isothiocyanate with microorganism	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/11/11 14:15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/00164

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Seeman P, Van Tol HH; "Dopamine receptor pharmacology"; Trends in Pharmacological Sciences 1994 Jul;15(7), pages 264-70	10-11
A	--	1-14
Y	Wise Roy A; "D-1-and D2-Type Contributions to Psychomotor Sensitization and Reward: Implications for Pharmacological Treatment Strategies"; Clinical Neuropharmacology (1995), Vol 18, Suppl 1, pages 74-83	12
A	--	1-14
Y	Bourland James A, French Edward D; "Effects of remoxipride, an atypical antipsychotic, on cocaine self-administration in the rat using fixed- and progressive-ratio schedules of reinforcement"; Drug and Alcohol Dependence (1995), Vol. 40, No. 2, pages 111-114	12
A	-- -----	1-14

INTERNATIONAL SEARCH REPORT
Information on patent family members

29/03/03

International application No.

PCT/SE 03/00164

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP	0367141	A2	09/05/90	SE 0367141 T3
				BR 1100204 A 01/08/00
				CN 1028104 B 05/04/95
				CN 1042537 A 30/05/90
				DE 68925405 D,T 27/06/96
				DK 168485 B 05/04/94
				DK 539789 A 01/05/90
				ES 2084594 T 16/05/96
				HK 1002706 A 00/00/00
				JP 2191256 A 27/07/90
				JP 2608788 B 14/05/97
				JP 2893175 B 17/05/99
				JP 2976282 B 10/11/99
				JP 7165720 A 27/06/95
				JP 10045717 A 17/02/98
				JP 10045718 A 17/02/98
				KR 138529 B 15/05/98
				MX 9202934 A 30/06/92
				US 5006528 A 09/04/91

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/00164

A. CLASSIFICATION OF SUBJECT MATTER

C07D 215/36, 215/227, 241/04, A61K 31/496, 31/4704,

IPC7: A61P 25/00, A61P 25/18, 25/14, 25/30, 9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0367141 A2 (OTSUKA PHARMACEUTICAL CO., LTD.), 9 May 1990 (09.05.90)	1-9,14
Y	--	10-12
X	Inoue Atsuko et al; "Aripiprazole, a novel antipsychotic drug, inhibits quinpirole-evoked GTPase activity but does not up-regulate dopamine D2 receptor following repeated treatment in the rat striatum"; European Journal of Pharmacology 321 (1997), pages 105-111.	1-9,14
Y	--	10-12

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

9 May 2003

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